



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification ⁶ : C07D 413/12, A61K 31/42, C07D 263/58, 417/12, 235/30 | | A1 | (11) International Publication Number: WO 98/40381 |
| | | (43) International Publication Date: 17 September 1998 (17.09.98) | |
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| (22) International Filing Date: 13 March 1998 (13.03.98) | | | |
| (30) Priority Data: 08/816,764 14 March 1997 (14.03.97) US 60/042,443 28 March 1997 (28.03.97) US | | | |
| (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/816,764 (CIP) Filed on 14 March 1997 (14.03.97) | | | |
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| | | Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. | |
| (54) Title: INHIBITORS OF IMPDH ENZYME | | | |
| (57) Abstract | | | |
| <p>The present invention relates to a novel class of compounds of formula (I) which are IMPDH inhibitors. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting IMPDH enzyme activity and consequently may be advantageously used as therapeutic agents for IMPDH mediated processes. This invention also relates to methods for inhibiting the activity of IMPDH using the compounds of formula (I) and related compounds, wherein A is a saturated, unsaturated or partially saturated monocyclic or bicyclic ring system optionally comprising up to 4 heteroatoms selected from N, O, and S wherein each A optionally comprises up to 4 substituents selected from R¹, R⁴ and R⁵; each R¹ is halogen, CN, NO₂, CF₃, OCF₃, OH, R³, OR³, 1,2-methylenedioxy, 1,2-ethylenedioxy, SR³, S(O)R³, SO₂R³, NH₂, NHR³, N(R³)₂, NR³R⁹, COOH, or COOR³; each R² is independently R¹ or a monocyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, and S, and wherein a CH₂ adjacent to said N, O or S may be substituted with C(O); and each R² optionally comprises up to 2 substituents, each substituent independently selected from R¹.</p> | | | |
| <p style="text-align: right;">(I)</p> | | | |

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INHIBITORS OF IMPDH ENZYME

TECHNICAL FIELD OF THE INVENTION

5 The present invention relates to a novel
class of compounds which inhibit IMPDH. This invention
also relates to pharmaceutical compositions comprising
these compounds. The compounds and pharmaceutical
compositions of this invention are particularly well
10 suited for inhibiting IMPDH enzyme activity and
consequently, may be advantageously used as therapeutic
agents for IMPDH mediated processes. This invention
also relates to methods for inhibiting the activity of
IMPDH using the compounds of this invention and related
15 compounds.

BACKGROUND OF THE INVENTION

The synthesis of nucleotides in organisms is
required for the cells in those organisms to divide and
replicate. Nucleotide synthesis in mammals may be
achieved through one of two pathways: the *de novo*
synthesis pathway or the salvage pathway. Different
cell types use these pathways to a different extent.

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Inosine-5'-monophosphate dehydrogenase (IMPDH; EC 1.1.1.205) is an enzyme involved in the *de novo* synthesis of guanosine nucleotides. IMPDH catalyzes the NAD-dependent oxidation of inosine-5'-monophosphate (IMP) to xanthosine-5'-monophosphate (XMP) [Jackson R.C. et. al., Nature, 256, pp. 331-333, (1975)].

IMPDH is ubiquitous in eukaryotes, bacteria and protozoa [Y. Natsumeda & S.F. Carr, Ann. N.Y. Acad., 696, pp. 88-93 (1993)]. The prokaryotic forms share 30-40% sequence identity with the human enzyme. Regardless of species, the enzyme follows an ordered Bi-Bi reaction sequence of substrate and cofactor binding and product release. First, IMP binds to IMPDH. This is followed by the binding of the cofactor NAD. The reduced cofactor, NADH, is then released from the complex, followed by the product, XMP [S.F. Carr et al., J. Biol. Chem., 268, pp. 27286-90 (1993); E.W. Holmes et al., Biochim. Biophys. Acta, 364, pp. 209-217 (1974)]. This mechanism differs from that of most other known NAD-dependent dehydrogenases, which have either a random order of substrate addition or require NAD to bind before the substrate.

Two isoforms of human IMPDH, designated type I and type II, have been identified and sequenced [F.R. Collart and E. Huberman, J. Biol. Chem., 263, pp. 15769-15772, (1988); Y. Natsumeda et. al., J. Biol. Chem., 265, pp. 5292-5295, (1990)]. Each is 514 amino acids, and they share 84% sequence identity. Both IMPDH type I and type II form active tetramers in solution, with subunit molecular weights of 56 kDa [Y. Yamada et. al., Biochemistry, 27, pp. 2737-2745 (1988)].

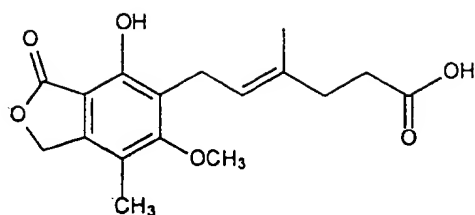
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The *de novo* synthesis of guanosine nucleotides, and thus the activity of IMPDH, is particularly important in B and T-lymphocytes. These cells depend on the *de novo*, rather than salvage pathway to generate sufficient levels of nucleotides necessary to initiate a proliferative response to mitogen or antigen [A.C. Allison et. al., Lancet II, 1179, (1975) and A.C. Allison et. al., Ciba Found. Symp., 48, 207, (1977)]. Thus, IMPDH is an attractive target for selectively inhibiting the immune system without also inhibiting the proliferation of other cells.

Immunosuppression has been achieved by inhibiting a variety of enzymes including for example, the phosphatase calcineurin (inhibited by cyclosporin and FK-506); dihydroorotate dehydrogenase, an enzyme involved in the biosynthesis of pyrimidines (inhibited by leflunomide and brequinar); the kinase FRAP (inhibited by rapamycin); and the heat shock protein hsp70 (inhibited by deoxyspergualin). [See B. D. Kahan, Immunological Reviews, 136, pp. 29-49 (1993); R. E. Morris, The Journal of Heart and Lung Transplantation, 12(6), pp. S275-S286 (1993)].

Inhibitors of IMPDH are also known. United States patents 5,380,879 and 5,444,072 and PCT publications WO 94/01105 and WO 94/12184 describe mycophenolic acid (MPA) and some of its derivatives as potent, uncompetitive, reversible inhibitors of human IMPDH type I ($K_i=33$ nM) and type II ($K_i=9$ nM). MPA has been demonstrated to block the response of B and T-cells to mitogen or antigen [A. C. Allison et. al., Ann. N. Y. Acad. Sci., 696, 63, (1993)].

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**MPA**

Immunosuppressants, such as MPA, are useful drugs in the treatment of transplant rejection and autoimmune diseases. [R. E. Morris, Kidney Intl., 49, Suppl. 53, S-26, (1996)]. However, MPA is characterized by undesirable pharmacological properties, such as gastrointestinal toxicity and poor bioavailability. [L. M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)].

Nucleoside analogs such as tiazofurin, ribavirin and mizoribine also inhibit IMPDH [L. Hedstrom, et. al. Biochemistry, 29, pp. 849-854 (1990)]. These compounds, which are competitive inhibitors of IMPDH, suffer from lack of specificity to this enzyme.

Mycophenolate mofetil, a prodrug which quickly liberates free MPA *in vivo*, was recently approved to prevent acute renal allograft rejection following kidney transplantation. [L. M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995); H. W. Sollinger, Transplantation, 60, pp. 225-232 (1995)]. Several clinical observations, however, limit the therapeutic potential of this drug. [L. M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)]. MPA is rapidly metabolized to the inactive glucuronide *in vivo*. [A.C., Allison and E.M. Eugui, Immunological Reviews, 136, pp. 5-28 (1993)].

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The glucuronide then undergoes enterohepatic recycling causing accumulation of MPA in the gastrointestinal tract where it cannot exert its IMPDH inhibitory activity on the immune system. This effectively lowers
5 the drug's *in vivo* potency, while increasing its undesirable gastrointestinal side effects.

It is also known that IMPDH plays a role in other metabolic events. Increased IMPDH activity has been observed in rapidly proliferating human leukemic
10 cell lines and other tumor cell lines, indicating IMPDH as a target for anticancer as well as immunosuppressive chemotherapy [M. Nagai et. al., Cancer Res., 51, pp. 3886-3890, (1991)]. IMPDH has also been shown to play a role in the proliferation of smooth muscle cells,
15 indicating that inhibitors of IMPDH, such as MPA or rapamycin, may be useful in preventing restenosis or other hyperproliferative vascular diseases [C. R. Gregory et al., Transplantation, 59, pp. 655-61 (1995); PCT publication WO 94/12184; and PCT publication WO
20 94/01105].

Additionally, IMPDH has been shown to play a role in viral replication in some viral cell lines. [S.F. Carr, J. Biol. Chem., 268, pp. 27286-27290 (1993)]. Analogous to lymphocyte and tumor cell lines,
25 the implication is that the *de novo*, rather than the salvage, pathway is critical in the process of viral replication.

The IMPDH inhibitor ribavirin is currently being evaluated for the treatment of hepatitis C virus
30 (HCV) and hepatitis B virus (HBV) infection and disease. Ribavirin enhances the sustained efficacy of interferon in HBV and HCV treatment. However, the therapeutic potential of ribavirin is limited by its

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lack of a sustained response in monotherapy and broad cellular toxicity.

Thus, there remains a need for potent IMPDH inhibitors with improved pharmacological properties.

- 5 Such inhibitors would have therapeutic potential as immunosuppressants, anticancer agents, antivascular hyperproliferative agents, antiinflammatory agents, antifungal agents, antipsoriatic and antiviral agents.

10 SUMMARY OF THE INVENTION

The present invention provides compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of IMPDH. These compounds can be used alone or in combination with other therapeutic
15 or prophylactic agents, such as antivirals, antiinflammatory agents, antibiotics, and immunosuppressants for the treatment or prophylaxis of transplant rejection and autoimmune disease. Additionally, these compounds are useful, alone or in
20 combination with other agents, as therapeutic and prophylactic agents for antiviral, antitumor, anticancer, antiinflammatory, antifungal, antipsoriatic, immunosuppressive, and restenosis therapy regimens.

- 25 The invention also provides pharmaceutical compositions comprising the compounds of this invention, as well as multi-component compositions comprising additional IMPDH compounds together with an immunosuppressant. The invention also provides methods
30 of using the compounds of this invention, as well as other related compounds, for the inhibition of IMPDH.

The compounds of this invention, as well as those used in the methods of this invention demonstrate

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a different metabolic profile than MPA and its derivatives. Because of this difference, methods of this invention and the compounds used therein may offer advantages as therapeutics for IMPDH mediated disease.

- 5 These advantages include increased overall therapeutic benefit and reduction in deleterious side effects.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described
10 may be more fully understood, the following detailed description is set forth. In the description, the following abbreviations are used:

| | <u>Designation</u> | <u>Reagent or Fragment</u> |
|----|--------------------|---------------------------------|
| 15 | Ac | acetyl |
| | Me | methyl |
| | Et | ethyl |
| | Bn | benzyl |
| | CDI | carbonyldiimidazole |
| 20 | DIEA | diisopropylethylamine |
| | DMAP | dimethylaminopyridine |
| | DMF | dimethylformamide |
| | DMSO | dimethylsulfoxide |
| | EDC | 1-(3-dimethylaminopropyl)-3- |
| 25 | | ethylcarbodiimide hydrochloride |
| | EtOAc | ethyl acetate |
| | THF | tetrahydrofuran |

The following terms are employed herein:

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Unless expressly stated to the contrary, the terms $-SO_2-$ and $-S(O)_2-$ as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinic ester.

5 The terms halo or halogen refer to a radical of fluorine, chlorine, bromine or iodine.

 The term immunosuppressant refers to a compound or drug which possesses immune response inhibitory activity. Examples of such agents include
10 cyclosporin A, FK506, rapamycin, leflunomide, deoxyspergualin, prednisone, azathioprine, mycophenolate mofetil, OKT3, ATAG, interferon and mizoribine.

 The term interferon refers to all forms of
15 interferons, including but not limited to alpha, beta and gamma forms.

 IMPDH-mediated disease refers to any disease state in which the IMPDH enzyme plays a regulatory role in the metabolic pathway of that disease. Examples of
20 IMPDH-mediated disease include transplant rejection and autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, and inflammatory bowel disease, as well as inflammatory diseases, cancer, viral replication diseases, and
25 vascular diseases.

 For example, the compounds, compositions and methods of using them of this invention may be used in the treatment of transplant rejection (e.g., kidney, liver, heart, lung, pancreas (islet cells), bone
30 marrow, cornea, small bowel and skin allografts and

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heart valve xenografts) and autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease (Crohn's disease, ulcerative colitis), lupus, diabetes, mellitus
5 myasthenia gravis, psoriasis, dermatitis, eczema, seborrhea, pulmonary inflammation, eye uveitis, hepatitis, Grave's disease, Hashimoto's thyroiditis, Behcet's or Sjorgen's syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, idiopathic
10 adrenal insufficiency, polyglandular autoimmune syndrome, and glomerulonephritis, scleroderma, lichen planus, viteligo (depigmentation of the skin), autoimmune thyroiditis, and alveolitis, inflammatory diseases such as osteoarthritis, acute pancreatitis,
15 chronic pancreatitis, asthma and adult respiratory distress syndrome, as well as in the treatment of cancer and tumors, such as solid tumors, lymphomas and leukemia, vascular diseases, such as restenosis, stenosis and arteriosclerosis, and viral DNA and RNA
20 replication diseases.

Additionally, IMPDH enzymes are also known to be present in bacteria and thus may regulate bacterial growth. As such, the IMPDH-inhibitor compounds, compositions and methods described herein
25 may be useful in treatment or prevention of bacterial infection, alone or in combination with other antibiotic agents.

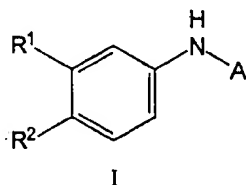
The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in
30 a patient or the improvement of an ascertainable measurement associated with a particular disorder. As

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used herein, the term "patient" refers to a mammal, including a human.

The terms "HBV", "HCV" and "HGV" refer to hepatitis-B, hepatitis-C and hepatitis-G virus,
5 respectively.

According to one embodiment, the invention provides methods of inhibiting IMPDH activity in a mammal comprising the step of administering to said mammal, a compound of formula I:



10 wherein:

A is a saturated, unsaturated or partially saturated monocyclic or bicyclic ring system optionally comprising up to 4 heteroatoms selected from N, O, and
15 S wherein each A optionally comprises up to 4 substituents selected from R¹, R⁴ and R⁵;

each R is halogen, CN, NO₂, CF₃, OCF₃, OH, R³, OR³, 1,2-methylenedioxy, 1,2-ethylenedioxy, SR³, S(O)R³, SO₂R³, NH₂, NHR³, N(R³)₂, NR³R⁹, COOH, or
20 COOR³;

each R² is independently R¹ or a monocyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, and S, and wherein a
25 CH₂ adjacent to said N, O or S maybe substituted with C(O); and each R² optionally comprises up to 2

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substituents, each substituent independently selected from R¹;

each R³ is independently (C₁-C₄)-straight or branched alkyl, or (C₂-C₄)-straight or branched alkenyl
 5 or alkynyl;

each R⁴ is independently (C₁-C₆)-straight or branched alkyl, or (C₂-C₆)-straight or branched alkenyl or alkynyl; and each R⁴ optionally comprises up to 2 substituents, wherein:

10 the first of said substituents, if present, is R¹, R⁵ or R⁸, and

the second of said substituents, if present, is R¹;

each R⁵ is independently selected from OR⁶,
 15 OC(O)R⁷, OC(O)R⁶, OC(O)OR⁷, OC(O)OR⁶, OC(O)N(R⁷)₂,
 OP(O)(OR⁷)₂, SR⁷, SR⁶, S(O)R⁷, S(O)R⁶, SO₂R⁷, SO₂R⁶,
 SO₂N(R⁷)₂, SO₂NR⁶R⁷, SO₃R⁷, C(O)R⁶, C(O)OR⁶, C(O)R⁷,
 C(O)OR⁷, NC(O)C(O)R⁷, NC(O)C(O)R⁶, NC(O)C(O)OR⁷,
 NC(O)C(O)N(R⁷)₂, C(O)N(R⁷)₂, C(O)N(OR⁷)R⁷,
 20 C(O)N(OR⁷)R⁶, C(NOR⁷)R⁷, C(NOR⁷)R⁶, N(R⁷)₂, NR⁷C(O)R⁶,
 NR⁷C(O)R⁷, NR⁶C(O)R⁶, NR⁷C(O)OR⁷, NR⁷C(O)OR⁶,
 NR⁷C(O)N(R⁷)₂, NR⁷C(O)NR⁶R⁷, NR⁷SO₂R⁷, NR⁷SO₂R⁶,
 NR⁷SO₂N(R⁷)₂, NR⁷SO₂NR⁶R⁷, N(OR⁷)R⁷, N(OR⁷)R⁶,
 P(O)(OR⁷)N(R⁷)₂, P(O)(OR⁷)₂, P(O)(N(R⁷)₂)₂, and
 25 P(O)(OR⁷)R⁷.

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R⁶ is a monocyclic or a bicyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, and S, and wherein a CH₂ adjacent
5 to any of said N, O, or S heteroatoms is optionally substituted with C(O); and each R⁶ optionally comprises up to 3 substituents, each substituent independently selected from R¹;

each R⁷ is independently H, (C₁-C₄)-straight or
10 branched alkyl, or (C₂-C₄) straight or branched alkenyl; and each R⁷ optionally comprises a substituent that is R⁸;

R⁸ is a monocyclic or a bicyclic ring system consisting of 5 to 6 members per ring, wherein said
15 ring system optionally comprises up to 4 heteroatoms selected from N, O, and S, and wherein a CH₂ adjacent to said N, O or S maybe substituted with C(O); and each R⁸ optionally comprises up to 2 substituents independently chosen from H, (C₁-C₄)-straight or
20 branched alkyl, (C₂-C₄) straight or branched alkenyl, 1,2-methylenedioxy, 1,2-ethylenedioxy and (CH₂)_n-R¹;

wherein n is 0, 1 or 2;

R⁹ is an amino protecting group; and

wherein any carbon atom in any R³, R⁴ or R⁷ is
25 optionally replaced by O, S, SO, SO₂, NH, or N(C₁-C₄)-alkyl.

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The term "substituted" refers to the replacement of one or more hydrogen radicals in a given structure with a radical selected from a specified group. When more than one hydrogen radical may be replaced with a substituent selected from the same specified group, the substituents may be either the same or different at every position.

The term "monocyclic or bicyclic ring system consisting of 5 to 6 members per ring" refers to 5 or 6 member monocyclic rings and 8, 9 and 10 membered bicyclic ring structures, wherein each bond in each ring may possess any degree of saturation that is chemically feasible. When such structures contain substituents, those substituents may be at any position of the ring system, unless otherwise specified.

As specified, such ring systems may optionally comprise up to 4 heteroatoms selected from N, O or S. Those heteroatoms may replace any carbon atoms in these ring systems as long as the resulting compound is chemically stable.

The term "amino protecting group" refers to a suitable chemical group which may be attached to a nitrogen atom. The term "protected" refers to when the designated functional group is attached to a suitable chemical group (protecting group). Examples of suitable amino protecting groups and protecting groups are described in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); L. Paquette, ed. Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons

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(1995) and are exemplified in certain of the specific compounds used in this invention.

Preferably, in methods employing the compounds of formula I, each A optionally comprises up to 4 substituents selected from R¹, R⁴ and R⁵, preferably wherein at least one substituent, if present, is selected from R⁴ and R⁵; also preferably wherein A comprises up to 4 substituents, each independently selected from R¹; and also preferably wherein A comprises up to 4 substituents, one substituent, if present, is selected from R⁴ and R⁵ and the remaining substituents, if present, are independently selected from R¹.

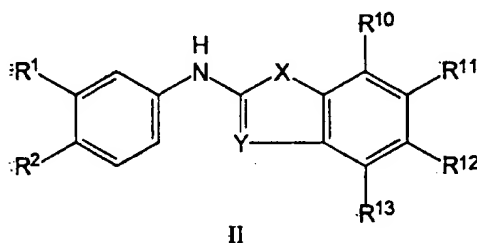
More preferably, in methods employing the compounds of formula I, A is a monocyclic aromatic ring system optionally comprising up to 4 heteroatom selected from N, O, and S wherein each A optionally comprises up to 4 substituents selected from R¹, R⁴ and R⁵, preferably wherein at least one substituent, if present, is selected from R⁴ and R⁵; also preferably wherein A comprises up to 4 substituents, each independently selected from R¹; and also preferably wherein A comprises up to 4 substituents, one substituent, if present, is selected from R⁴ and R⁵ and the remaining substituents, if present, are independently selected from R¹.

Also more preferably, in methods employing the compounds of formula I, A is a bicyclic aromatic

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ring system optionally comprising up to 4 heteroatoms selected from N, O, and S, wherein each A optionally comprises up to 4 substituents selected from R¹, R⁴ and R⁵, preferably wherein at least one substituent, if present, is selected from R⁴ and R⁵; also preferably wherein A comprises up to 4 substituents, each independently selected from R¹; and also preferably wherein A comprises up to 4 substituents, one substituent, if present, is selected from R⁴ and R⁵ and the remaining substituents, if present, are independently selected from R¹.

More preferably, in methods employing the compounds of formula I, are those methods wherein the compound has the structure of the formula:



15

wherein:

R¹⁰, R¹¹, R¹² and R¹³ are each independently selected from R¹ and R⁴, wherein only one of R¹⁰, R¹¹, R¹² and R¹³ may simultaneously be R⁴; and

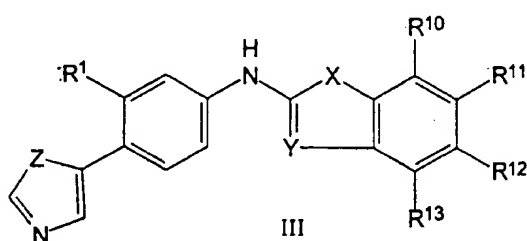
X and Y are independently selected from CH₂, CHR³, CHR⁴, O, S, NH, NR³, NR⁴, CH, CR³, CR⁴, and N.

The present invention also provides compounds which are useful in inhibiting IMPDH. According to one

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embodiment, the compounds have the structure and definitions of formula I above. Preferably, the invention provides compounds with the structure and definitions of formula II above.

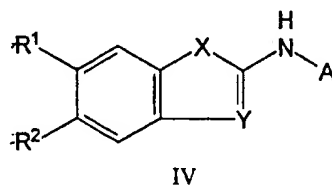
5 More preferably, the invention provides a compound of formula III:



10 wherein

R¹, R¹⁰, R¹¹, R¹², R¹³, X and Y are as defined in formula II and Z is O, S, NH or NR³, wherein R³ is as defined in formula I.

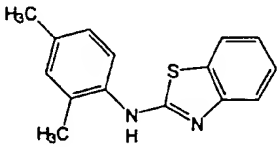
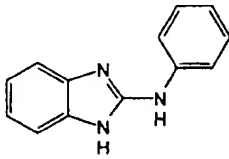
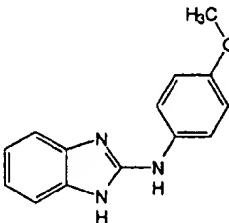
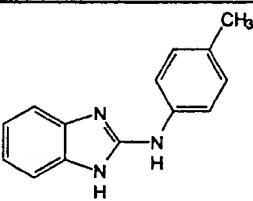
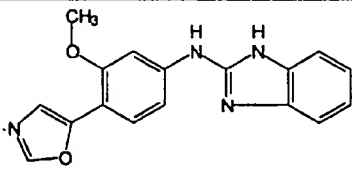
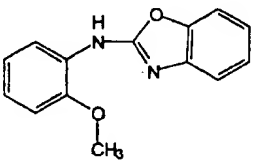
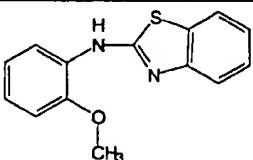
15 According to an alternate embodiment, the invention provides a compound of the formula IV:

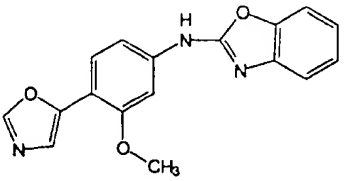
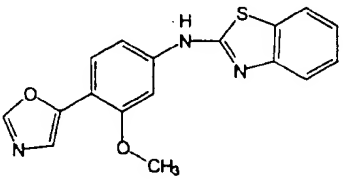
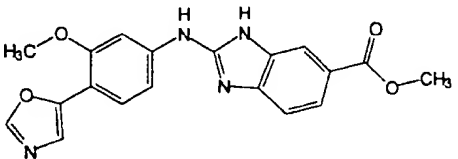
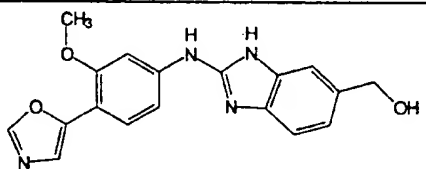
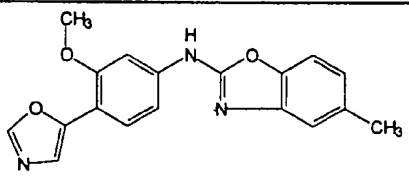
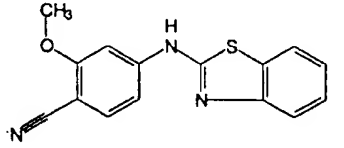
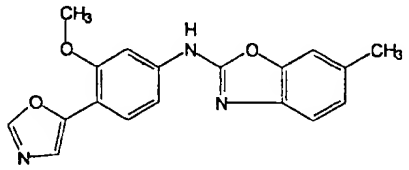
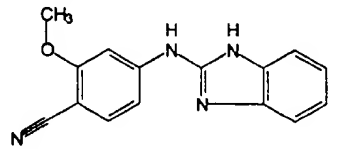


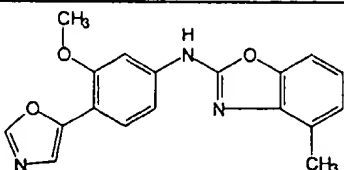
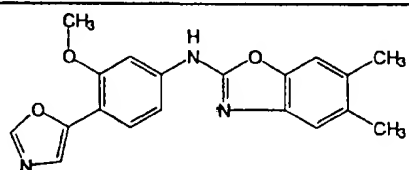
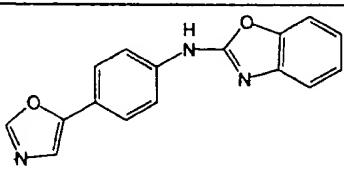
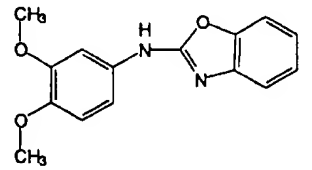
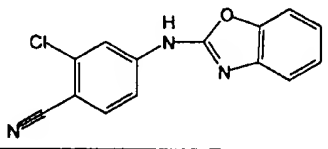
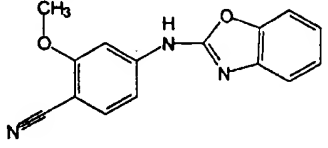
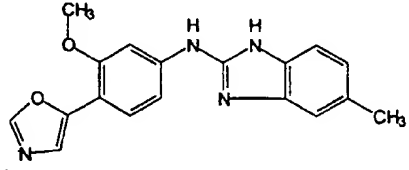
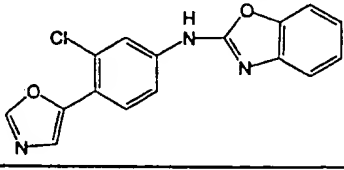
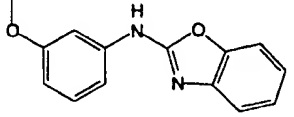
wherein R¹, R², A, X and Y are as defined for formula II.

20 Table I lists preferred individual compounds of the invention and preferred compounds employed in the compositions and methods of this invention.

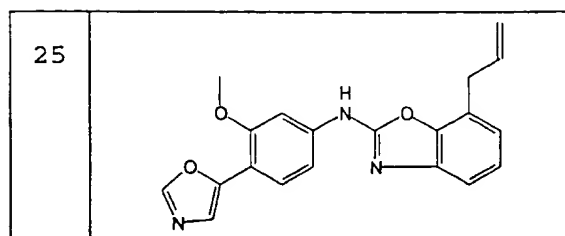
Table I

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The compounds of this invention may contain
5 one or more asymmetric carbon atoms and thus may occur
as racemates and racemic mixtures, single enantiomers,
diastereomeric mixtures and individual diastereomers.
All such isomeric forms of these compounds are
expressly included in the present invention. Each
10 stereogenic carbon may be of the R or S configuration.

Combinations of substituents and variables
envisioned by this invention are only those that result
in the formation of stable compounds. The term
"stable", as used herein, refers to compounds which
15 possess stability sufficient to allow manufacture and
which maintains the integrity of the compound for a
sufficient period of time to be useful for the purposes
detailed herein (e.g., therapeutic or prophylactic
administration to a mammal or for use in affinity
20 chromatography applications). Typically, such
compounds are stable at a temperature of 40 °C or less,
in the absence of moisture or other chemically reactive
conditions, for at least a week.

As used herein, the compounds of this
25 invention, including the compounds of formulae I-IV,
are defined to include pharmaceutically acceptable

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derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species. Preferred prodrugs include derivatives where a group which enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae I-IV.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-

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naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and
5 undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

10 Salts derived from appropriate bases include alkali metal (e.g., sodium, potassium), alkaline earth metal (e.g., magnesium), ammonium and N-(C₁₋₄ alkyl)₄⁺ salts.

This invention also envisions the
15 quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

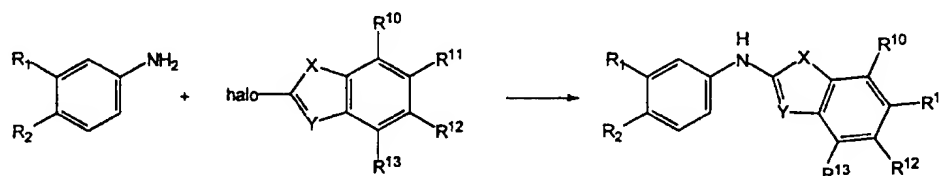
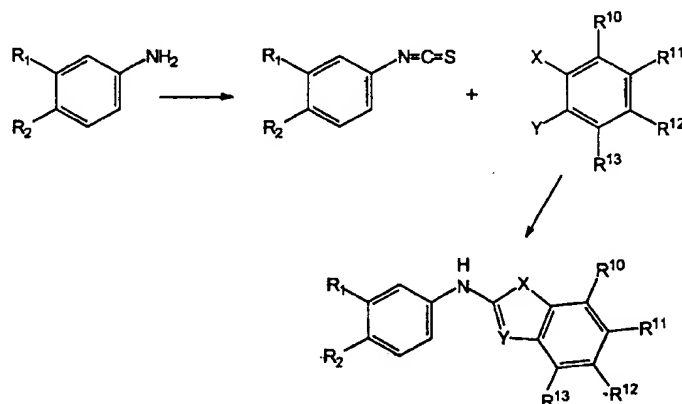
The compounds of this invention may be
20 synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials.

In general, compounds of formula I-IV are conveniently obtained via methods illustrated in
25 General Synthetic Schemes 1-2.

In General Synthetic Scheme 1 (see below), an A, B, C, D-substituted aniline is reacted with an R¹⁰, R¹¹, R¹², R¹³-substituted halo-substituted heterocycle under standard conditions to give the desired amine.

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In this process, A, B, C, D and R¹⁰, R¹¹, R¹², R¹³ may be one or more independent substituents (or their suitably protected variants) as exemplified by the ring substituents listed for compounds of formulae I-IV above, at any position on the aromatic ring. Additionally, the halo leaving group may alternatively be any suitable equivalent, for example, mesylate or tosylate.

Scheme 1Scheme 2

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An alternate synthetic route is illustrated in General Synthetic Scheme 2 (see above). An R¹, R²-substituted aniline is converted to the corresponding thioisocyanate under standard conditions. This product is then treated with an aniline, where

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R¹⁰, R¹¹, R¹², R¹³ may be one or more independent substituents (or their suitably protected variants) as exemplified by the ring substituents listed for compounds of formulae I-IV above, at any position on the aromatic ring and X and Y are as exemplified in the compounds of formulae I-IV, to give the desired substituted amine products.

As can be appreciated by the skilled artisan, the above synthetic schemes are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described above may be performed in an alternate sequence or order to give the desired compounds.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The novel compounds of the present invention are ligands for IMPDH. Accordingly, these compounds are capable of targeting and inhibiting IMPDH enzyme.

- 25 -

Inhibition can be measured by various methods, including, for example, IMP dehydrogenase HPLC assays (measuring enzymatic production of XMP and NADH from IMP and NAD) and IMP dehydrogenase spectrophotometric
5 assays (measuring enzymatic production of NADH from NAD). [See C. Montero et al., Clinica Chimica Acta, 238, pp. 169-178 (1995)].

Pharmaceutical compositions of this invention comprise a compound of formula I or IV or a
10 pharmaceutically acceptable salt thereof; an additional agent selected from an immunosuppressant, an anticancer agent, an antiviral agent, antiinflammatory agent, antifungal agent, antibiotic, or an antivasular hyperproliferation compound; and any pharmaceutically
15 acceptable carrier, adjuvant or vehicle. Alternate compositions of this invention comprise a compound of formulae I-IV or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier, adjuvant or vehicle. Such composition may optionally
20 comprise an additional agent selected from an immunosuppressant, an anticancer agent, an antiviral agent, antiinflammatory agent, antifungal agent, antibiotic, or an antivasular hyperproliferation compound.

25 The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when

- 26 -

administered in doses sufficient to deliver a therapeutic amount of the compound.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as α -tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α -, β -, and γ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl- β -cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of formulae I-IV.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by

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inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending

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medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of

5 injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as those described in

10 Pharmacopeia Helvetica, Ph. Helv., or a similar alcohol, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly

15 used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of

20 formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions,

25 dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents

30 include lactose and dried corn starch. When aqueous

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suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening
5 and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of
10 this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa
15 butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For
20 application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention
25 include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream
30 containing the active compound suspended or dissolved

- 30 -

in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, 5 benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also 10 included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical 15 formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

20 Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 75 mg/kg body weight per day of the IMPDH inhibitory compounds described herein are useful in a monotherapy and/or in combination therapy for the 25 prevention and treatment of IMPDH mediated disease. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic 30 or acute therapy. The amount of active ingredient that

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may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 5 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

When the compositions of this invention comprise a combination of an IMPDH inhibitor of 10 formulae I-IV and one or more additional therapeutic or prophylactic agents, both the IMPDH inhibitor and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 to 80% of the dosage normally administered in 15 a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this 20 invention in a single composition.

According to one embodiment, the pharmaceutical compositions of this invention comprise an additional immunosuppression agent. Examples of additional immunosuppression agents include, but are 25 not limited to, cyclosporin A, FK506, rapamycin, leflunomide, deoxyspergualin, prednisone, azathioprine, mycophenolate mofetil, OKT3, ATAG, interferon and mizoribine.

According to an alternate embodiment, the 30 pharmaceutical compositions of this invention may

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additionally comprise an anticancer agent. Examples of anticancer agents include, but are not limited to, cis-platin, actinomycin D, doxorubicin, vincristine, vinblastine, etoposide, amsacrine, mitoxantrone, 5 teniposide, taxol, colchicine, cyclosporin A, phenothiazines, interferon and thioxantheres.

According to another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an antiviral agent. Examples of 10 antiviral agents include, but are not limited to, Cytovene, Ganciclovir, trisodium phosphonoformate, Ribavirin, d4T, ddI, A T, and acyclovir.

According to yet another alternate embodiment, the pharmaceutical compositions of this 15 invention may additionally comprise an antivasular hyperproliferative agent. Examples of antivasular hyperproliferative agents include, but are not limited to, HMG Co-A reductase inhibitors such as lovastatin, thromboxane A2 synthetase inhibitors, eicosapentanoic 20 acid, ciprostone, trapidil, ACE inhibitors, low molecular weight heparin, mycophenolic acid, rapamycin and 5-(3'-pyridinylmethyl)benzofuran-2-carboxylate.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or 25 combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been 30 alleviated to the desired level, treatment should

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cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

As the skilled artisan will appreciate, lower
5 or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health
10 status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician.

In an alternate embodiment, this invention
15 provides methods of treating or preventing IMPDH mediated disease in a mammal comprising the step of administering to said mammal any of the pharmaceutical compositions and combinations described above. If the pharmaceutical composition only comprises the IMPDH
20 inhibitor of this invention as the active component, such methods may additionally comprise the step of administering to said mammal an agent selected from an antiinflammatory agent, immunosuppressant, an anticancer agent, an antiviral agent, or an
25 antivasular hyperproliferation compound. Such additional agent may be administered to the mammal prior to, concurrently with, or following the administration of the IMPDH inhibitor composition.

In a preferred embodiment, these methods are
30 useful in suppressing an immune response in a mammal.

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Such methods are useful in treating or preventing diseases, including, transplant rejection (e.g., kidney, liver, heart, lung, pancreas (islet cells), bone marrow, cornea, small bowel and skin allografts and heart valve xenografts), graft versus host disease, 5 and autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease (Crohn's disease, ulcerative colitis), lupus, diabetes, mellitus myasthenia gravis, 10 psoriasis, dermatitis, eczema, seborrhoea, pulmonary inflammation, eye uveitis, hepatitis, Grave's disease, Hashimoto's thyroiditis, Behcet's or Sjorgen's syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, idiopathic adrenal insufficiency, 15 polyglandular autoimmune syndrome, glomerulonephritis, scleroderma, lichen planus, viteligo (depigmentation of the skin), autoimmune thyroiditis, and alveolitis.

These methods comprise the step of administering to the mammal a composition comprising a 20 compound of any of formulae I-IV and a pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an additional immunosuppressant and a pharmaceutically 25 acceptable adjuvant.

Alternatively, this method comprises the step of administering to said mammal a composition comprising a compound of formulae I-IV; an additional immunosuppressive agent and a pharmaceutically 30 acceptable adjuvant.

In an alternate preferred embodiment, these methods are useful for inhibiting viral replication in a mammal. Such methods are useful in treating or

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preventing DNA and RNA viral diseases caused by, for example, HTLV-1 and HTLV-2, HIV-1 and HIV-2, nasopharyngeal carcinoma virus, yellow fever, dengue fever, HBV, HCV, HGV, yellow fever virus, dengue fever virus, Japanese encephalitis virus, human papilloma virus, rhinoviruses and Herpes viruses, such as Epstein-Barr, cytomegaloviruses, Herpes Simplex, Types 1 and 2, or Type 6. [See, United States patent 5,380,879].

10 These methods comprise the step of administering to the mammal a composition comprising a compound of any of formulae I-IV, and a pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an additional antiviral agent and a pharmaceutically acceptable adjuvant.

 Alternatively, this method comprises the step of administering to said mammal a composition comprising a compound of formulae I-IV; an additional antiviral agent and a pharmaceutically acceptable adjuvant.

 In another alternate preferred embodiment, these methods are useful for inhibiting vascular cellular hyperproliferation in a mammal. Such methods are useful in treating or preventing diseases, including, restenosis, stenosis, arteriosclerosis and other hyperproliferative vascular disease.

 These methods comprise the step of administering to the mammal a composition comprising a compound of any of formulae I-IV, and a

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pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an additional antivasculard
5 hyperproliferative agent and a pharmaceutically acceptable adjuvant.

Alternatively, this method comprises the step of administering to said mammal a composition comprising a compound of formulae I-IV; an additional
10 antivasculard hyperproliferative agent and a pharmaceutically acceptable adjuvant.

In another alternate preferred embodiment, these methods are useful for inhibiting tumors and cancer in a mammal. Such methods are useful in
15 treating or preventing diseases, including, tumors and malignancies, such as lymphoma, leukemia and other forms of cancer.

These methods comprise the step of administering to the mammal a composition comprising a
20 compound of any of formulae I-IV, and a pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an additional antitumor or
25 anticancer agent and a pharmaceutically acceptable adjuvant.

Alternatively, this method comprises the step of administering to said mammal a composition comprising a compound of formulae I-IV; an additional
30 antitumor or anticancer agent and a pharmaceutically acceptable adjuvant.

In another alternate preferred embodiment,

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these methods are useful for inhibiting inflammation and inflammatory diseases in a mammal. Such methods are useful in treating or preventing diseases, including, osteoarthritis, acute pancreatitis, chronic
5 pancreatitis, asthma and adult respiratory distress syndrome.

These methods comprise the step of administering to the mammal a composition comprising a compound of any of formulae I-IV, and a
10 pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an antiinflammatory agent and a pharmaceutically acceptable adjuvant.

15 In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

20

General Materials and Methods

All temperatures are recorded in degrees Celsius. Thin layer chromatography (TLC) was carried out using 0.25 mm thick E. Merck silica gel 60 F₂₅₄
25 plates and elution with the indicated solvent system. Detection of the compounds was carried out by treating the plate with an appropriate visualizing agent, such as 10% solution of phosphomolybdic acid in ethanol or a 0.1% solution of ninhydrin in ethanol, followed by
30 heating, and/or by exposure to UV light or iodine

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vapors when appropriate. Analytical HPLC was carried out using a Rainin Mycrosorb-MV, 5 μ Cyano reverse phase column, 3.9mm x 150mm, with a flow rate of 1.0mL/minute and a solvent gradient of 5-100% acetonitrile (0.1%
5 TFA) in water (0.1% TFA). HPLC retention times were recorded in minutes. NMR spectral data was acquired using a Bruker AMX500 in the indicated solvent.

The IMP dehydrogenase HPLC assay follows our standard conditions for the enzymatic production of XMP
10 and NADH from IMP and NAD, but utilizes high pressure liquid chromatography on a C18 column with ion pairing reagents to separate all four components. The extent of reaction is then determined from the resulting product peak areas. This assay is particularly useful
15 for determining the inhibition profiles of compounds which have significant absorbance in the UV-visible region between 290 and 340 nm.

The reaction mixture typically contains 0.1 M KPi; pH 8.0, 0.1M KCl, 0.5 mM EDTA, 2 mM DTT, and 0.2
20 mM each of IMP and NAD. This solution is incubated at 37°C for 10 minutes. The reaction is started by the addition of enzyme to a final concentration of 20 to 100 nM, and is allowed to proceed for 10 minutes. After the allotted time, the reaction is quenched by
25 the addition of mycophenolic acid to a final concentration of 0.01 mM.

The extent of conversion is monitored by HPLC using a Rainin Microsorb ODS column C18-200 of dimensions 4.6 X 10 mm and a solvent system containing

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tetrabutylammonium sulfate (5mM) in 0.1 M KPi pH 6.0 with a 0-30% methanol gradient over 15 minutes. A similar solvent system has been used previously for the purification of halo-IMP derivatives. [L. C. Antionio
5 and J. C. Wu, Biochemistry, 33, 1753-1759 (1994).] A UV-monitor set at 254 nM is used to detect the four components, and the product peaks are integrated to determine the extent of conversion of the substrates.

For the analysis of inhibitors, the compound
10 in question is dissolved in DMSO to a final concentration of 20 mM and added to the initial assay mixture at the desired concentration in a volume of 2-5% (v/v). The reaction is started by the addition of enzyme and after 10 minutes is quenched as above.
15 After HPLC analysis, the product areas are used to determine the extent of conversion relative to a control assay containing only DMSO and no test compound. IC50 or Ki values are determined from non linear least squares fitting of conversion vs
20 concentration curves to the tight-binding equations of Henderson. [P. J. F. Henderson, Biochem. J., 127, 321 (1972).]

We have measured the inhibition constants of each compound against IMPDH using an adaptation of the
25 method first reported by Magasanik. [B. Magasanik, H. S. Moyed, and L. B. Gehring J. Biol. Chem., 226, p.339 (1957)].

Insofar as compounds of formulae I-IV are able to inhibit IMPDH, they are of evident clinical
30 utility for the treatment of IMPDH mediated disease.

- 40 -

These tests are predictive of the compounds ability to inhibit IMPDH in vivo.

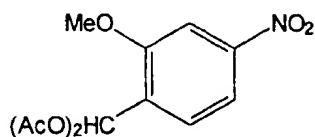
Experimental Section

5 Synthesis of Representative Examples:

Example 1

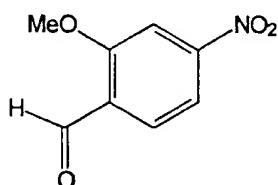
Synthesis of Compound 5

10

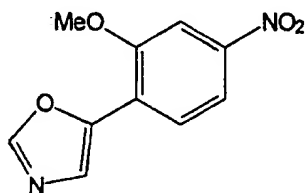
**A1**

To a solution of glacial acetic acid (95mL),
15 acetic anhydride (95mL, 1mole) and 2-methoxy-4-nitrotoluene (10g, 50mmole) at 0°C was added conc. H₂SO₄ (14.2mL) in a dropwise fashion. Upon complete addition, CrO₃ (16.67g, 167mmole) was added portion-wise over 120 mins. Following an additional 15 mins of
20 stirring at 0°C, the reaction mixture was poured over ice and the resulting precipitate was isolated by filtration, rinsing with cold H₂O. Purification by flash chromatography, eluting with a gradient of 15-50% EtOAc in hexanes, provided 8.14g (51%) **A1** as a white
25 solid. The ¹H NMR was consistent with that of the desired structure.

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**A2**

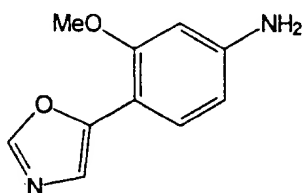
A stirred suspension of **A1** (81.94g, 307mmole) in
5 dioxane (100mL) was treated with concentrated HCl
(20mL) and heated at reflux overnight. Upon cooling to
ambient temperature, the product **A2** precipitated as a
light yellow crystalline solid in a yield of 40.65g
(73.1%). The filtrate was concentrated to a volume of
10 ca. 80mL and a second crop of product crystals was
driven from solution by the addition of hexanes,
yielding 8.91g (16.0%). Both batches were identical by
¹H NMR and TLC analysis and were consistent with that
of the desired material. The total yield of **A2** was
15 49.56g (89.1%).

**A3**

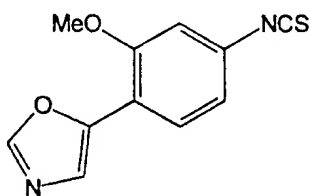
A solution of **A2** (456mg, 2.51mmole), tosylmethyl
20 isocyanide (490mg, 2.51mmole) and K₂CO₃ (347mg,
251mmole) were dissolved in methanol and heated to
reflux for 1.5 hours. The product mixture was then
concentrated *in vacuo*, redissolved in CH₂Cl₂, washed

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with water and brine, dried over Na_2SO_4 and again concentrated in vacuo. Purified product **A3** was obtained through recrystallization (Et_2O /hexanes) to yield 375mg (68%). The ^1H NMR was consistent with that of the desired structure.

**A4**

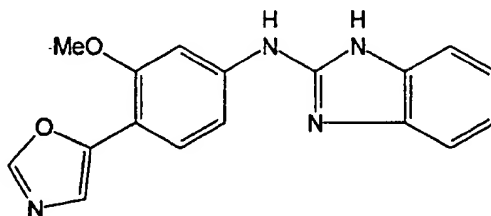
10 A solution of **A3** (4.214g, 19.1mmole) in EtOAc (150mL) was treated with 10%Pd/C (1.05g, 25 wt.% of **A3**) and subjected to 40psi H_2 (g) (Parr Hydrogenation Apparatus) overnight. The reaction mixture was filtered and concentrated in vacuo. Pure product **A4**
15 was obtained through flash chromatography, eluting with a gradient of 30-40% EtOAc/hexanes, in a yield of 3.4g (93%). The ^1H NMR was consistent with that of the desired structure.

**A5**

20

- 43 -

A solution of **A4** (250mg, 1.3 mmoles) in 10 mL of methylene chloride was treated with 1, 1'-thiocarbonyldi-2(1H)-pyridone (302mg, 1.3 mmoles). The resulting solution was stirred at room temperature for 10 min., and then washed once with water and once with 0.5 N HCl. The organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The resulting oil **A5** was used immediately.



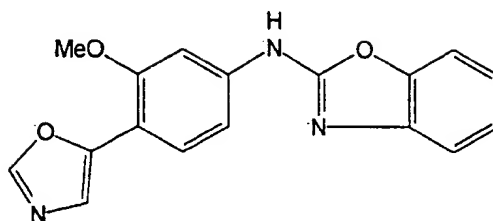
5

Compound **A5** (1.3 mmoles) in 44 mL of benzene was treated with phenylene diamine (140mg, 1.3 mmoles). The resulting solution was heated to reflux for 15 min., at which time 405mg (1.95 mmoles) of dicyclohexylcarbodiimide was added. Refluxing was continued for 5 h. After cooling to room temperature a precipitate **5** was isolated by filtration (270 mg, 68% for 2 steps). Mass spectral analysis was consistent with that of the desired structure. ^1H NMR (500MHz, d_6 -DMSO) δ 11 (s, 1H), 9.7 (s, 1H), 8.3 (s, 1H), 7.65 (d, 2H), 7.55 (d, 1H), 7.4 (s, 1H), 7.3 (bd, 2H), 7.0 (bs, 2H), 3.95 (s, 3H).

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Example 2

Synthesis of Compound 8



5

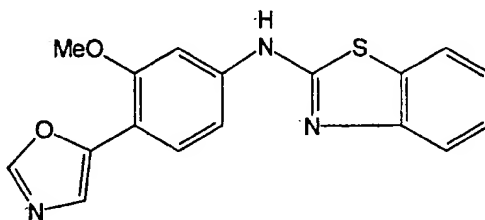
8

A solution of **A4** (500mg, 2.63 mmol) and 2-chlorobenzoxazole (0.2 ml, 1.75 mmol) in DMF (2 mL) was heated to 100 °C and stirred overnight. The reaction mixture was diluted with ethyl acetate and 2N HCl. The layers were partitioned and the organic extracts dried over MgSO₄. The organics were concentrated in vacuo and the residue purified via medium pressure liquid chromatograph (elution with 1:99 MeOH/CH₂Cl₂) to give 54 mgs (13%) of **8** as a light yellow solid; TLC: R_f = 0.20 (3:97 MeOH/CH₂Cl₂). ¹HNMR (500 MHz, CDCl₃) δ 9.2 (bs), 8.0 (s), 7.85 (d), 7.7-7.55 (m), 7.45 (d), 7.35-7.1 (m) 4.15 (s).

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Example 3

Synthesis of Compound 9



5

9

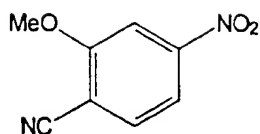
A solution of **A4** (500mg, 2.63 mmol) and 2-chlorobenzothiazole (0.2 ml, 1.5 mmol) in DMF (2 mL) was heated to 100 °C and stirred overnight. The reaction mixture was diluted with ethyl acetate and 2N HCl. The layers were partitioned and the organic extracts dried over MgSO₄. The organics were concentrated in vacuo and the residue purified via medium pressure liquid chromatograph (elution with 1:99 MeOH/CH₂Cl₂) to give 176 mgs (41%) of **9** as a light yellow solid; TLC: R_f = 0.23 (3:97 MeOH/CH₂Cl₂). ¹HNMR (500 MHz, CDCl₃) δ 8.1 (bs), 8.0 (s), 7.85 (d), 7.75 (d), 7.6 (s), 7.5 (s), 7.45 (t), 7.25 (t), 7.15 (d), 4.1 (s).

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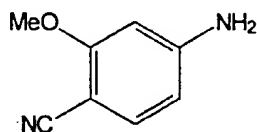
Example 4

Synthesis of Compound 15

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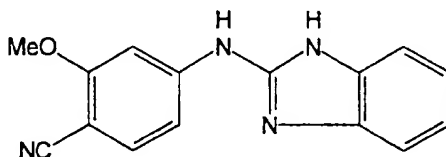
**B1**

A solution of 2-bromo-5-nitroanisole (1.0g, 4.3mmol) and copper(I)cyanide (388mg, 4.3mmol) in DMF (5mL) was heated to 150°C for four hours. The product mixture was cooled to ambient temperature and poured into water. The resulting precipitate was filtered, dissolved in CH₂Cl₂, dried (MgSO₄) and concentrated to yield a tan solid **B1** in a yield of 634mg (83%). The ¹H NMR was consistent with that of the desired structure.

**B2**

B1 (192mg, 1.08mmol) and SnCl₂•2H₂O (729mg, 3.23mmol) were combined in ethanol (5mL) and heated to 75°C for a period of one hour. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate, and washed with saturated NaHCO₃ (aq, diluted with 2N NaOH to break emulsion, 2x's) and water (1x). Dried (MgSO₄) and concentrated to yield an orange solid **B2** in a yield of 140mg (88%). The ¹H NMR was consistent with that of the desired structure.

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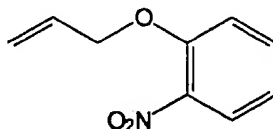
15

Compound 15 was prepared in a fashion analogous to
5 that of compound 5 wherein B2 (50mg, 0.34mmol) gave
rise to 15 in a yield of 46.5mg (52%). TLC: R_f = 0.22
(60% EtOAc in hexanes). ^1H NMR (500 MHz, CDCl_3) δ 11.24
(s, 1H), 10.12 (s, 1H), 7.68 (s, 1H), 7.61 (d, 1H),
7.52 (d, 1H), 7.41 (bd, 1H), 7.32 (bd, 1H), 7.05 (m,
10 2H), 3.92 (s, 3H).

Example 5

Synthesis of Compound 25

15

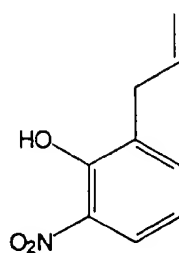


C1

To a solution of 2-nitrophenol (45mmol) in DMF
20 (10mL) was added powdered K_2CO_3 (56mmol) and allyl
bromide (55mmol). The mixture was stirred at ambient
temperature for one hour, diluted with ether and washed
with water (3xs) and brine (1x). The resulting product

- 48 -

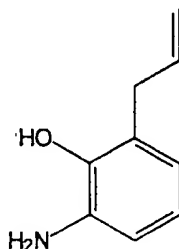
solution was dried (Na_2SO_4), and concentrated to yield C1 which was utilized with no further purification.



C2

5

C2 (45mmol, neat) was heated overnight at 180°C under nitrogen. Upon cooling to ambient temperature, the crude product mixture was taken up in ether and extracted with 2N NaOH(aq). This aqueous portion was cooled to 0°C, acidified (2N HCl) and extracted with ether. The extracts were washed with brine, dried (Na_2SO_4), and concentrated to yield C2 (15.5mmol). The ^1H NMR was consistent with that of the desired structure.



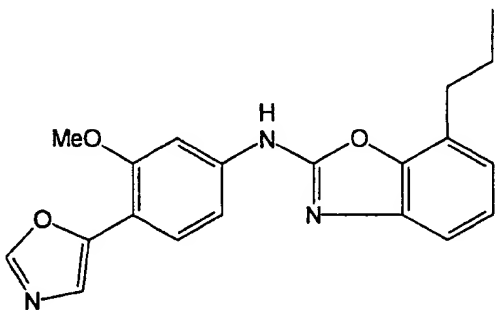
C3

15

C3 (2.2mmol) was dissolved in ethanol and treated with iron (powder, 11mmol) and conc. HCl (1mL) with heating to reflux overnight. The mixture was cooled to

- 49 -

ambient temperature, decanted, basified with NaHCO_3 (aq) and extracted with ethyl acetate. The extracts were washed with brine, dried (Na_2SO_4), and concentrated to provide a brown oil. Purification by silica gel chromatography (eluting with 20% ethyl acetate in hexanes) gave **C3** in a yield of 248mg, 1.2mmol, 76%) as a dark oil. The ^1H NMR was consistent with that of the desired structure.



10

25

Compound **25** was prepared in a fashion analogous to that of compound **5** wherein **C3** (78mg, 0.526mmol) and **A5** (0.53mmol) gave rise to **25** in a yield of 24mg (13%).

15 TLC: R_f = 0.28 (3% CH_3OH in CH_2Cl_2). ^1H NMR (500 MHz, CDCl_3) δ 9.73(br s, 1H), 8.11(s, 1H), 7.89(d, 1H), 7.78(d, 1H), 7.54(dd, 1H), 7.47(s, 1H), 7.34(d, 1H), 7.20(t, 1H), 7.00(d, 1H), 6.08(m, 1H), 5.10(m, 2H), 4.08(s, 3H), 3.60(d, 2H).

20

- 50 -

Example 6

IMPDH Activity Inhibition Assay

5 We measured the inhibition constants of the compounds listed in Table II utilizing the following protocol:

 IMP dehydrogenase activity was assayed following an adaptation of the method first reported by
10 Magasanik. [Magasanik, B. Moyed, H. S. and Gehring L. B. (1957) J. Biol. Chem. 226, 339]. Enzyme activity was measured spectrophotometrically, by monitoring the increase in absorbance at 340 nm due to the formation of NADH (ϵ_{340} is $6220 \text{ M}^{-1} \text{ cm}^{-1}$). The reaction mixture
15 contained 0.1 M Tris pH 8.0, 0.1 M KCl, 3 mM EDTA, 2 mM DTT, 0.1 M IMP and enzyme (IMPDH human type II) at a concentration of 15 to 50 nM. This solution is incubated at 37°C for 10 minutes. The reaction is started by adding NAD to a final concentration of 0.1M
20 and the initial rate is measured by following the linear increase in absorbance at 340 nm for 10 minutes. For reading in a standard spectrophotometer (path length 1 cm) the final volume in the cuvette is 1.0 ml. The assay has also been adapted to a 96 well microtiter
25 plate format; in this case the concentrations of all the reagents remain the same and the final volume is decreased to 200 μl .

 For the analysis of inhibitors, the compound in question is dissolved in DMSO to a final concentration
30 of 20 mM and added to the initial assay mixture for preincubation with the enzyme at a final volume of 2-

- 51 -

5% (v/v). The reaction is started by the addition of NAD, and the initial rates measured as above. K_i determinations are made by measuring the initial velocities in the presence of varying amounts of inhibitor and fitting the data using the tight-binding equations of Henderson (Henderson, P. J. F. (1972) Biochem. J. 127, 321].

These results are shown in Table II. K_i values are expressed in nM. Category "A" indicates 0.01 to 500 nm activity, category "B" indicates 501-5,000 nm activity, category "C" indicates 5,001 to 15,000 nm activity, category "D" indicates greater than 15,000 nm activity. The designation "ND" is used where a given compound was not tested.

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Table II

| | Cmpd # | K _i (nM) |
|----|--------|---------------------|
| 5 | 1 | ND |
| | 2 | D |
| | 3 | D |
| | 4 | D |
| 10 | 5 | B |
| | 6 | D |
| | 7 | D |
| | 8 | A |
| | 9 | A |
| 15 | 10 | A |
| | 11 | B |
| | 12 | A |
| | 13 | C |
| | 14 | A |
| 20 | 15 | C |
| | 16 | A |
| | 17 | A |
| | 18 | D |
| | 19 | D |
| 25 | 20 | D |
| | 21 | D |
| | 22 | B |
| | 23 | B |
| | 24 | D |
| 30 | 25 | A |

Example 15

35

Anti-Viral Assays

The antiviral efficacy of compounds may be evaluated in various in vitro and in vivo assays. For example, compounds may be tested in in vitro viral replication assays. In vitro assays may employ whole cells or isolated cellular components. In vivo assays

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include animal models for viral diseases. Examples of such animal models include, but are not limited to, rodent models for HBV or HCV, the Woodchuck hepatitis model for HBV, and chimpanzee HCV infection.

5

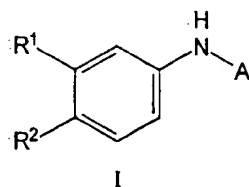
While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and methods of
10 this invention.

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CLAIMS

We claim:

1. A method of inhibiting IMPDH activity in
 5 a mammal comprising the step of administering to said
 mammal a compound of the formula:



wherein:

- A is a saturated, unsaturated or partially
 10 saturated monocyclic or bicyclic ring system optionally
 comprising up to 4 heteroatoms selected from N, O, and
 S wherein each A optionally comprises up to 4
 substituents selected from R¹, R⁴ and R⁵;

- each R¹ is halogen, CN, NO₂, CF₃, OCF₃, OH, R³,
 15 OR³, 1,2-methylenedioxy, 1,2-ethylenedioxy, SR³,
 S(O)R³, SO₂R³, NH₂, NHR³, N(R³)₂, NR³R⁹, COOH, or
 COOR³;

- each R² is independently R¹ or a monocyclic ring
 system consisting of 5 to 6 members per ring, wherein
 20 said ring system optionally comprises up to 4
 heteroatoms selected from N, O, and S, and wherein a
 CH₂ adjacent to said N, O or S maybe substituted with
 C(O); and each R² optionally comprises up to 2
 substituents, each substituent independently selected
 25 from R¹;

- 55 -

each R³ is independently (C₁-C₄)-straight or branched alkyl, or (C₂-C₄)-straight or branched alkenyl or alkynyl;

each R⁴ is independently (C₁-C₆)-straight or branched alkyl, or (C₂-C₆)-straight or branched alkenyl or alkynyl; and each R⁴ optionally comprises up to 2 substituents, wherein:

the first of said substituents, if present, is R¹, R⁵ or R⁸, and

the second of said substituents, if present, is R¹;

each R⁵ is independently selected from OR⁶, OC(O)R⁷, OC(O)R⁶, OC(O)OR⁷, OC(O)OR⁶, OC(O)N(R⁷)₂, OP(O)(OR⁷)₂, SR⁷, SR⁶, S(O)R⁷, S(O)R⁶, SO₂R⁷, SO₂R⁶, SO₂N(R⁷)₂, SO₂NR⁶R⁷, SO₃R⁷, C(O)R⁶, C(O)OR⁶, C(O)R⁷, C(O)OR⁷, NC(O)C(O)R⁷, NC(O)C(O)R⁶, NC(O)C(O)OR⁷, NC(O)C(O)N(R⁷)₂, C(O)N(R⁷)₂, C(O)N(OR⁷)R⁷, C(O)N(OR⁷)R⁶, C(NOR⁷)R⁷, C(NOR⁷)R⁶, N(R⁷)₂, NR⁷C(O)R⁶, NR⁷C(O)R⁷, NR⁶C(O)R⁶, NR⁷C(O)OR⁷, NR⁷C(O)OR⁶, NR⁷C(O)N(R⁷)₂, NR⁷C(O)NR⁶R⁷, NR⁷SO₂R⁷, NR⁷SO₂R⁶, NR⁷SO₂N(R⁷)₂, NR⁷SO₂NR⁶R⁷, N(OR⁷)R⁷, N(OR⁷)R⁶, P(O)(OR⁷)N(R⁷)₂, and P(O)(OR⁷)₂;

R⁶ is a monocyclic or a bicyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms

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selected from N, O, and S, and wherein a CH₂ adjacent to any of said N, O, or S heteroatoms is optionally substituted with C(O); and each R⁶ optionally comprises up to 3 substituents, each substituent independently
5 selected from R¹;

each R⁷ is independently H, (C₁-C₄)-straight or branched alkyl, or (C₂-C₄) straight or branched alkenyl; and each R⁷ optionally comprises a substituent that is R⁸;

10 R⁸ is a monocyclic or a bicyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, and S, and wherein a CH₂ adjacent to said N, O or S maybe substituted with C(O); and each
15 R⁸ optionally comprises up to 2 substituents independently chosen from H, (C₁-C₄)-straight or branched alkyl, (C₂-C₄) straight or branched alkenyl, 1,2-methylenedioxy, 1,2-ethylenedioxy and (CH₂)_n-R¹;

wherein n is 0, 1 or 2;

20 R⁹ is an amino protecting group; and

wherein any carbon atom in any R³, R⁴ or R⁷ is optionally replaced by O, S, SO, SO₂, NH, or N(C₁-C₄)-alkyl.

25 2. The method according to claim 1, wherein in said compound, A is a monocyclic aromatic ring system optionally comprising up to 4 heteroatom

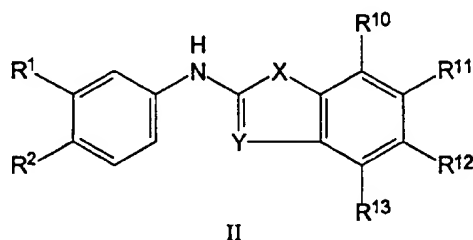
- 57 -

selected from N, O, and S wherein each A optionally comprises up to 4 substituents selected from R^1 , R^4 and R^5 .

5 3. The method according to claim 1, wherein in said compound, A is a bicyclic aromatic ring system optionally comprising up to 4 heteroatoms selected from N, O, and S, wherein each A optionally comprises up to 4 substituents selected from R^1 , R^4 and R^5 .

10

4. The method according to claim 1, wherein said compound has the structure of the formula:



15 wherein

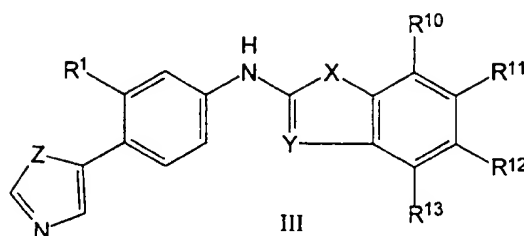
R^{10} , R^{11} , R^{12} and R^{13} are each independently selected from R^1 and R^4 , wherein only one of R^{10} , R^{11} , R^{12} and R^{13} may simultaneously be R^4 ; and

X and Y are independently selected from CH_2 ,

20 CHR^3 , CHR^4 , O, S, NH, NR^3 , and NR^4 .

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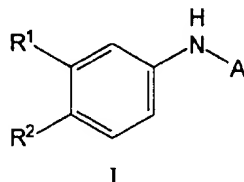
5. A compound of the formula:
wherein:



5

R^1 , R^{10} , R^{11} , R^{12} , R^{13} , X and Y are as defined in claim 4 and Z is O, S, NH or NR^3 , wherein R^3 is as defined in claim 1.

10 6. A pharmaceutical composition comprising:
a. a compound of formula



in an amount effective to inhibit IMPDH activity,
wherein A, R^1 and R^2 are as defined in claim 1;

15 b. an additional agent selected from
an immunosuppressant, an anti-cancer agent, an anti-viral agent, antiinflammatory agent, antifungal agent, antibiotic, or an anti-vascular hyperproliferation agent;

20 c. a pharmaceutically acceptable adjuvant.

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7. The composition according to claim 6,
wherein in said compound, A is a monocyclic aromatic
ring system optionally comprising up to 4 heteroatom
selected from N, O, and S wherein each A optionally
5 comprises up to 4 substituents selected from R¹, R⁴ and
R⁵.

8. The composition according to claim 6,
wherein in said compound, A is a bicyclic aromatic ring
10 system optionally comprising up to 4 heteroatoms
selected from N, O, and S, wherein each A optionally
comprises up to 4 substituents selected from R¹, R⁴ and
R⁵.

15 9. A pharmaceutical composition comprising:
a. a compound according to claim 5 in
an amount effective to inhibit IMPDH activity; and
b. a pharmaceutically acceptable
adjuvant.

20

10. The pharmaceutical composition according
to claim 9, additionally comprising an additional agent
selected from an immunosuppressant, an anti-cancer
agent, an anti-viral agent, antiinflammatory agent,
25 antifungal agent, antibiotic, or an anti-vascular
hyperproliferation agent.

11. A method for treating or preventing
IMPDH mediated disease in a mammal comprising the step

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of administering to said mammal a composition according to claim 6.

12. A method for treating or preventing
5 IMPDH mediated disease in a mammal comprising the step of administering to said mammal a composition according to claim 9.

13. The method according to claim 12,
10 wherein said composition additionally comprises an agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, antiinflammatory agent, antifungal agent, antibiotic, or an anti-vascular hyperproliferation agent
15

14. The method according to any one of claims
11 to 13, wherein said method is used to suppress an immune response and wherein said additional agent, if present, is an immunosuppressant.
20

15. The method according to claim 14,
wherein said IMPDH mediated disease is an autoimmune disease.

16. The method according to any one of
25 claims 11 to 13, wherein the IMPDH mediated disease is a viral disease and wherein said additional agent, if present, is an anti-viral agent.

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17. The method according to any one of
claims 11 to 13, wherein the IMPDH mediated disease is
a vascular disease and wherein said additional agent,
if present, is an anti-vascular hyperproliferation
5 agent.

18. The method according to any one of
claims 11 to 13, wherein the IMPDH mediated disease is
cancer and wherein said additional agent, if present,
10 is an anti-cancer agent.

19. The method according to any one of claims
11 to 13, wherein the IMPDH mediated disease is an
inflammatory disease and wherein said additional agent,
15 if present, is an anti-inflammatory agent.

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/US 98/04932

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D413/12 A61K31/42 C07D263/58 C07D417/12 C07D235/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | US 5 536 747 A (PATTERSON JOHN W ET AL) 16 July 1996 see column 89-90; claim 1 --- | 5-10 |
| A | DE 22 21 866 A (ELY LILLY) 7 December 1972 see page 24-28 --- | 5-10 |
| A | GB 1 171 904 A (UNILEVER) 26 November 1969 see page 1 --- | 5-10 |
| A | F. MERCHAN ET AL.: "Synthesis of 2-Aryliminoimidazolidines and 2-Arylamino benzimidazoles from Methyl N-Aryldithiocarbamates" SYNTHESIS, vol. 6, 1982, pages 482-484, XP002065887 see table 1 ----- | 5-10 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 May 1998

Date of mailing of the international search report

09.07.98

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/04932

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-4, 11-19
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 98/04932

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 1-4,11-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Claims Nos.: 1-4, 11-19

Although claims 1-4, 11-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/04932

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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